



THE UNIVERSITY *of* EDINBURGH

## Edinburgh Research Explorer

### Can serotonin agonists unlock age-dependent failure of liver regeneration?

**Citation for published version:**

Wigmore, SJ 2011, 'Can serotonin agonists unlock age-dependent failure of liver regeneration?', *Journal of Hepatology*, vol. 55, no. 6, pp. 1455-6. <https://doi.org/10.1016/j.jhep.2011.05.017>

**Digital Object Identifier (DOI):**

[10.1016/j.jhep.2011.05.017](https://doi.org/10.1016/j.jhep.2011.05.017)

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Publisher's PDF, also known as Version of record

**Published In:**

Journal of Hepatology

**Publisher Rights Statement:**

Available under Open Access

**General rights**

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

**Take down policy**

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact [openaccess@ed.ac.uk](mailto:openaccess@ed.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.



# Can serotonin agonists unlock age-dependent failure of liver regeneration?

Stephen J. Wigmore\*

MRC Centre for Inflammation Research, Queen's Medical Research Institute, University of Edinburgh, 49 Little France Crescent, Edinburgh EH16 4TJ, UK; Scottish Liver Transplant Unit, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, UK

## COMMENTARY ON:

**Serotonin reverts age-related capillarization and failure of regeneration in the liver through a VEGF-dependent pathway. Furrer K, Rickenbacher A, Tian Y, Jochum W, Bittermann AG, K  ch A, Humar B, Graf R, Moritz W, Clavien PA. *Proc Natl Acad Sci USA*. 2011 Feb 15;108(7):2945–2950. Copyright (2011). Abstract reprinted with the permission of the National Academy of Sciences of the United States of America.**

<http://www.ncbi.nlm.nih.gov/pubmed/21282654>

**Abstract:** The function of the liver is well-preserved during the aging process, although some evidence suggests that liver regeneration might be impaired with advanced age. We observed a decreased ability of the liver to restore normal volume after partial hepatectomy in elderly mice, and we identified a pathway that rescued regeneration and was triggered by serotonin. 2,5-dimethoxy-4-iodoamphetamine (DOI), a serotonin receptor agonist, reversed the age-related pseudocapillarization of old liver and improved hepatosinusoidal blood flow. After hepatectomy, the open fenestrae were associated with a restored attachment of platelets to endothelium and the initiation of a normal regenerative response, including the up-regulation of essential growth mediators and serotonin receptors. In turn, hepatocyte proliferation recovered along with regain of liver volume and animal survival. DOI operates through the release of VEGF, and its effects could be blocked with anti-VEGF antibodies both *in vitro* and *in vivo*. These results suggest that pseudocapillarization in the aged acts as a barrier to liver regeneration. DOI breaks this restraint through an endothelium-dependent mechanism driven by VEGF. This pathway highlights a target for reversing the age-associated decline in the capacity of the liver to regenerate.

   2011 Published by Elsevier B.V. on behalf of the European Association for the Study of the Liver.

The liver is a remarkable organ which can regenerate after major surgery or injury in the adult. In a previous study the group from Zurich headed by Professor Pierre Alain-Clavien published a

ground-breaking paper demonstrating that in a mouse model, liver regeneration could be stimulated by serotonin carried by blood borne platelets [1]. Serotonin was found to act through receptors expressed by liver tissue and mice with impaired platelet responses had defective liver regeneration. Treatment of these mice with a serotonin agonist ‘rescued’ this deficiency and allowed liver regeneration to occur. These novel observations lead to the possibility that therapeutic treatment with serotonin receptor agonists might be a possible strategy to augment liver regeneration.

In their most recent paper published in *PNAS*, the Zurich group have gone on to study the effect of aging on serotonin pathways and liver regeneration. Furrer *et al.* elegantly demonstrate deficient liver regeneration in aged mice that have been subjected to 70% hepatectomy [2]. Mechanistic insight into this observation is provided through novel associations with failure of expression of serotonin receptors, a loss of endothelial fenestration in the hepatic sinusoids and increased mortality related to a failure of hepatic regeneration. Both the inadequacy of serotonin receptor expression and the process of loss of fenestration, termed pseudocapillarization, is reversible by treating animals with a serotonin receptor agonist 2,5 dimethoxy-4-iodoamphetamine (DOI). In addition, they show that DOI affects expression of a number of candidate mediators but has greatest effect on expression of vascular endothelial growth factor (VEGF). They further show that DOI treated animals that are exposed to anti VEGF antibody have a diminished regenerative response after liver resection. Based on these observations, Furrer *et al.* propose a model where loss of fenestration in aging sinusoids limits access of regenerative molecules to hepatocytes and suggest that DOI may reverse this process by improving fenestration via VEGF [2].

The proposed model would certainly explain their findings but as with many other novel studies it also raises new questions. The purpose of fenestrations is not fully understood. Moreover, the processes that lead to pseudocapillarization in old age also remain obscure. In the context of the current paper the normalcy of serotonin concentrations in aging mice and the development of pseudocapillarization seem to partly conflict with the effects of serotonin agonists in reversing pseudocapillarization in this model. Further it would be interesting to understand the nature of the serotonin-VEGF-fenestration axis in development or in the livers of young animals. Data supporting a VEGF-fenestration axis as a mechanism for the effects of serotonin or DOI are strong; however, it is not beyond the bounds of possibility that there may

Received 22 February 2011; received in revised form 29 April 2011; accepted 17 May 2011

\* Address: MRC Centre for Inflammation Research, Queen's Medical Research Institute, University of Edinburgh, 49 Little France Crescent, Edinburgh EH16 4TJ, UK. Tel.: +44 131 242 3615; fax: +44 131 242 3617.

E-mail addresses: [s.wigmore@ed.ac.uk](mailto:s.wigmore@ed.ac.uk), [v1swigmo@staffmail.ed.ac.uk](mailto:v1swigmo@staffmail.ed.ac.uk)



## International Hepatology

be effects on other pathways relevant to regeneration. It is known for example that old age is associated with changes in the proportion of cells at different stages in the cell cycle. Specifically, old age is associated with fewer cells in G1/S phase and this in turn might be associated with an impaired response to regeneration stimuli. Serotonin is known to affect cell growth and development; however, data on this are at times conflicting. It would be interesting to know what the impact of serotonin or serotonin agonists is on the hepatocyte cell cycle.

The study by Furrer *et al.* focuses on 2-year-old mice and we cannot tell from the information given whether loss of endothelial fenestration is a gradual process that continues through adulthood and at what stage this becomes significant in terms of regenerative responses. Similarly, we can only estimate the age equivalency of the 2-year-old mouse in human years. These questions become important when we try to relate this research to the human clinical situation. The majority of patients who undergo liver resection in the West would be considered elderly and yet failure of liver regeneration even after major hepatectomy is rarely a clinical problem [3,4]. In a similar vein, liver regeneration after split liver transplant or liver resection is rarely a problem in patients with thrombocytopenia. So what exactly is the role of platelets and serotonin in liver regeneration in man? These questions remain unanswered however there is no doubt that serotonin is a remarkable molecule. This molecule that is produced largely by enterochromaffin cells in the gut has been implicated in bone health [5], regulating beta cell mass in pregnancy [6], psychiatric disease and even as the trigger for locusts to swarm [7].

That serotonin should be a potential target for drug development is no surprise given the compelling data provided by the Clavien group in their current paper published in PNAS [2] and in previous publications [1]. In the paper by Furrer *et al.*, DOI is associated with increased serotonin receptor expression by hepatocytes and with increased fenestration of sinusoidal endothelial cells. Both changes could potentially affect liver regeneration but which is more important? An alternative view would say that since both are potentially beneficial the science does not matter, it is the effect that is important. As scientists and doctors we do

however, like to know these things – particularly since serotonin agonists have been implicated in promoting fibrotic responses [8] and since VEGF inhibitors are currently in use in treating colorectal cancer [9]. And so it is likely that further work will need to be done before serotonin receptor antagonists find their way into the formulary of the liver surgeon.

### Conflict of interest

The author declared he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

### References

- [1] Lesurtel M, Graf R, Aleil B, Walther D, Tian Y, Jochum W, et al. Platelet-derived serotonin mediates liver regeneration. *Science* 2006;312:104–107.
- [2] Furrer K, Rickenbacher A, Tian Y, Jochum W, Bittermann AG, Käch A, et al. Serotonin reverts age-related capillarization and failure of regeneration in the liver through a VEGF-dependent pathway. *Proc Natl Acad Sci USA* 2011, [Epub ahead of print].
- [3] Cho SW, Steel J, Tsung A, Marsh JW, Geller DA, Gamblin TC. Safety of liver resection in the elderly: how important is age? *Ann Surg Oncol* 2010, [Epub ahead of print].
- [4] Menon KV, Al-Mukhtar A, Aldouri A, Prasad RK, Lodge PA, Toogood GJ. Outcomes after major hepatectomy in elderly patients. *J Am Coll Surg* 2006;203:677–683.
- [5] Collet C, Schiltz C, Geoffroy V, Maroteaux L, Launay JM, de Vernejoul MC. The serotonin 5-HT2B receptor controls bone mass via osteoblast recruitment and proliferation. *FASEB J* 2008;22:418–427.
- [6] Kim H, Toyofuku Y, Lynn FC, Chak E, Uchida T, Mizukami H, et al. Serotonin regulates pancreatic beta cell mass during pregnancy. *Nat Med* 2010;16:804–808.
- [7] Anstey ML, Rogers SM, Ott SR, Burrows M, Simpson SJ. Serotonin mediates behavioral gregarization underlying swarm formation in desert locusts. *Science* 2009;323:627–630.
- [8] Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 2007;356:39–46.
- [9] Hubbard J, Grothey A. Antiangiogenesis agents in colorectal cancer. *Curr Opin Oncol* 2010;22:374–380.